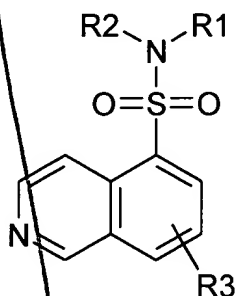


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We claim:

1. A method for promoting survival of substantia nigra neuronal cells comprising contacting the cells with a trophic amount of a *ptc* therapeutic.
2. A method for promoting survival of dopaminergic cells comprising contacting the cells with a trophic amount of a *ptc* therapeutic.
3. A method for promoting survival of GABAergic cells comprising contacting the cells with a trophic amount of a *ptc* therapeutic.
4. A method for the treating a disorder characterized by loss of dopaminergic and/or GABAergic neurons which comprises administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.
5. A method for the treating or preventing Parkinson's disease comprising administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.
6. A method for the treating or preventing Huntington's disease comprising administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.
7. The method of any of claims 1-6, wherein the *ptc* therapeutic binds to *patched* and mimics *hedgehog*-mediated *patched* signal transduction.
8. The method of claim 7, wherein the *ptc* therapeutic is a small organic molecule.
9. The method of claim 7, wherein the binding of the *ptc* therapeutic to *patched* results in upregulation of *patched* and/or *gli* expression.
10. The method of any of claims 1-6, wherein the *ptc* therapeutic is a small organic molecule which interacts with neuronal cells to mimic *hedgehog*-mediated *patched* signal transduction.
11. The method of any of claims 1-6, wherein the *ptc* therapeutic mimics *hedgehog*-mediated *patched* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in a *patched* signal pathway.
12. The method of any of claims 1-6, wherein the *ptc* therapeutic alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in the intracellular signal transduction pathway of *patched*.

13. The method of claim 12, wherein the *ptc* therapeutic is an antisense construct which inhibits the expression of a protein which is involved in the signal transduction pathway of *patched* and the expression of which antagonizes *hedgehog*-mediated signals.
14. The method of claim 13, wherein the antisense construct is an oligonucleotide of about 20-30 nucleotides in length and having a GC content of at least 50 percent.
15. The method of claim 14, wherein the antisense oligonucleotide is selected from the group consisting of: 5'-GTCCTGGCGCCGCCGCCGCCGTCGCC;
5'-TTCCGATGACCGGCCTTTCGCGGTGA; and
5'-GTGCACGGAAAGGTGCAGGCCACACT
16. The method of claims 12, wherein the *ptc* therapeutic is a small organic molecule which binds to *patched* and regulates *patched*-dependent gene expression.
17. The method of claim 11, wherein the *ptc* therapeutic is an inhibitor of protein kinase A.
18. The method of claim 17, wherein the PKA inhibitor is a 5-isoquinolinesulfonamide
19. The method of claim 18, wherein the PKA inhibitor is represented in the general formula:



wherein,

R_1 and R_2 each can independently represent hydrogen, and as valence and stability permit a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O$ - $(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$, or

R_1 and R_2 taken together with N form a heterocycle (substituted or unsubstituted);

R_3 is absent or represents one or more substitutions to the isoquinoline ring such as a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-$
5 R_8 , $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$;

R_8 represents a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

10 n and m are independently for each occurrence zero or an integer in the range of 1 to 6.

20. The method of claim 17, wherein the PKA inhibitor is cyclic AMP analog.

21. The method of claim 17, wherein the PKA inhibitor is selected from the group consisting of N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 1-(5-isoquinoline-sulfonyl)-2-methylpiperazine, KT5720, 8-bromo-cAMP, dibutyryl-cAMP and PKA Heat
15 Stable Inhibitor isoform α .

22. The method of any of claims 4-6, wherein patient is being treated prophylactically.

23. A therapeutic preparation of a small molecule antagonist of *patched*, which *patched* antagonist is provided in a pharmaceutically acceptable carrier and in an amount sufficient to promote survival of dopaminergic cells in a mammal.

20 24. A therapeutic preparation of a small molecule antagonist of *patched*, which *patched* antagonist is provided in a pharmaceutically acceptable carrier and in an amount sufficient to promote survival of dopaminergic cells in an adult human.

25. The preparation of claim 24, which *patched* antagonist binds to *patched*.

26. The preparation of claim 24, wherein the *patched* antagonist is provided in an amount sufficient to produce sufficient to promote survival of dopaminergic cells in a mammal treated with MPTP at 1mg/kg..
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27. The preparation of claim 24, wherein the *patched* antagonist is provided in an amount sufficient to produce sufficient to promote survival of dopaminergic cells in a mammal treated with MPTP at 10mg/kg..

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40.

A method for limiting damage to neuronal cells by Parkinsonian conditions, comprising administering to a patient a gene activation construct which recombines with a genomic *hedgehog* gene of the patient to provide a heterologous transcriptional regulatory sequence operatively linked to a coding sequence of the *hedgehog* gene.

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41.

An isolated and/or recombinantly produced polypeptide comprising an amino acid sequence which is at least 95 percent identical to a sequence represented by SEQ ID. NO. 16 or 17, or a bioactive extracellular fragment thereof.

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An isolated and/or recombinantly produced polypeptide encoded by a nucleic acid which hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID. NO. 16 and SEQ ID. NO. 17.

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43.

An isolated and/or recombinantly produced *Dhh* hedgehog polypeptide, or a bioactive extracellular fragment thereof, encoded by a human *Dhh* gene.

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44.

An isolated and/or recombinantly produced *Ihh* hedgehog polypeptide, or a bioactive extracellular fragment thereof, encoded by a human *Ihh* gene.

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45.

(new) The polypeptide of any of claims 41-44, formulated in a pharmaceutically acceptable carrier.

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46.

(new) The polypeptide of any of claims 41-44, wherein the polypeptide is purified to at least 80% by dry weight.

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47.

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48.

An isolated nucleic acid encoding a polypeptide comprising a *hedgehog* amino acid sequence which is at least 95 percent identical to a *hedgehog* protein selected from the group consisting of SEQ ID No:16 and SEQ ID No:17, and fragments thereof, which *hedgehog* amino acid sequence (i) binds to a *patched* protein, (ii) regulates differentiation of neuronal cells, (iii) regulates survival of differentiated neuronal cells, (iv) regulates proliferation of chondrocytes, (v) regulates proliferation of testicular germ line cells, or (vi) functionally replaces drosopholia hedgehog in transgenic drosophila fly, or a combination thereof.

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48.

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An isolated nucleic acid encoding a polypeptide having a *hedgehog* amino acid sequence encoded by a nucleic acid which hybridizes under stringent conditions to a nucleic acid sequence selected from the group consisting of SEQ ID No:7 and SEQ ID No:8, which *hedgehog* amino acid sequence of the polypeptide corresponds to a natural proteolytic product of a hedgehog protein and (i) binds to a *patched* protein, (ii) regulates differentiation of neuronal cells, (iii) regulates survival of differentiated neuronal cells, (iv) regulates proliferation of chondrocytes, (v) regulates proliferation of testicular germ line

cells, or (vi) functionally replaces drosopholia hedgehog in transgenic drosophila fly, or a combination thereof.

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49. The nucleic acid of claim 47 or 48, wherein the *hedgehog* amino acid sequence is identical to a *hedgehog* protein selected from the group consisting of SEQ ID No:16 and SEQ ID No:17.

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50. An isolated nucleic acid comprising a coding sequence of a human *hedgehog* gene, encoding a bioactive *hedgehog* protein.

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51. An expression vector, capable of replicating in at least one of a prokaryotic cell and eukaryotic cell, comprising the nucleic acid of claim 47, 48 or 50.

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52. A host cell transfected with the expression vector of claim 51 and expressing said recombinant polypeptide.

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53. A method of producing a recombinant *hedgehog* polypeptide comprising culturing the cell of 52 in a cell culture medium to express a *hedgehog* polypeptide and isolating said *hedgehog* polypeptide from said cell culture.

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54. A recombinant transfection system, comprising

- (i) a gene construct including the nucleic acid of claim 47, 48 or 50, operably linked to a transcriptional regulatory sequence for causing expression of the *hedgehog* polypeptide in eukaryotic cells, and
- (ii) a gene delivery composition for delivering said gene construct to a cell and causing the cell to be transfected with said gene construct.

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55. The recombinant transfection system of claim 54, wherein the gene delivery composition is selected from a group consisting of a recombinant viral particle, a liposome, and a polycationic nucleic acid binding agent,

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56. A probe/primer comprising a substantially purified oligonucleotide, said oligonucleotide containing a region of nucleotide sequence which hybridizes under stringent conditions to at least 10 consecutive nucleotides of sense or antisense sequence of SEQ ID No. 7 or 8, or naturally occurring mutants thereof.

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57. The probe/primer of claim 56, wherein the probe/primer further comprises a label group attached thereto and able to be detected.

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58. A test kit for detecting cells which contain a *hedgehog* mRNA transcript, comprising a probe/primer of claim 57.

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- add
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THE
JOURNAL
OF THE
ROYAL ANTHROPOLOGICAL INSTITUTE
VOL. LXXV.
PART I.
1905.